$= 4F^2/\sigma^2(F^2)$ where the uncertainty factor, p, was set to the value of 0.04.

Scattering factors were taken from Cromer and Waber.[5] Anomalous effects were included in F_c for all non-hydrogen atoms.[6] The values for $\Delta F'$ and $\Delta F''$ were those of Cromer.[7] Only 1149 reflections with intensities greater than 3.0 times their standard deviation were used in the refinements. The final cycle of refinement included 169 variable parameters and converged with unweighted and weighted agreement factors of

$$R_1 = \sum||F_o| - |F_c||/\sum F_o = 0.05$$

$$R_2 = (\sum w(|F_o| - |F_c|)^2/\sum wF_o^2)^{1/2} = 0.054$$

The standard deviation of an observation unit weight was 1.73. There was one correlation coefficient greater than 0.5. The highest peak in the final difference Fourier had a height of 0.76 e/Å^3, with an estimated error base on $\sigma(F)$ of 0.13.[8] The minimum negative peak had a height of −0.55 e/Å^3, with an estimated error based on $\sigma(F)$ of 0.13. Plots of $\sum w(|F_o| - |F_c|)^2$ vs $|F_o|$, reflection order in data collection $\sin\theta/\lambda$, and various classes of indices showed no unusual trends. All calculations were performed on a VAX computer using SDP/VAX.[9]

Acknowledgment. The help provided by Dr. M. Bruck, Molecular Structure Lab, and Professor John H. Enemark, Department of Chemistry, University of Arizona, in solving the crystal structure of the nickel complex is gratefully acknowledged. Part of the crystal structure determination was a class project of Ms. Firestone in Chemistry 517. We also thank Professor Robert B. Bates for many helpful discussions.

Supplementary Material Available: Tables of additional positional parameters, bond distances, and bond angles for $[NiPyPySe_2(H_2O)_2][ClO_4]\cdot CH_3NO_2$ (5 pages); observed and calculated structure factors (6 pages). Ordering information is given on any current masthead page.

Concerning Model Metabolites of the Carcinogen 4-Nitroquinoline 1-Oxide. Reactivity and Solvolytic Behavior of 1-Hydroxy-4-(acetoxyimino)-1,4-dihydroquinoline

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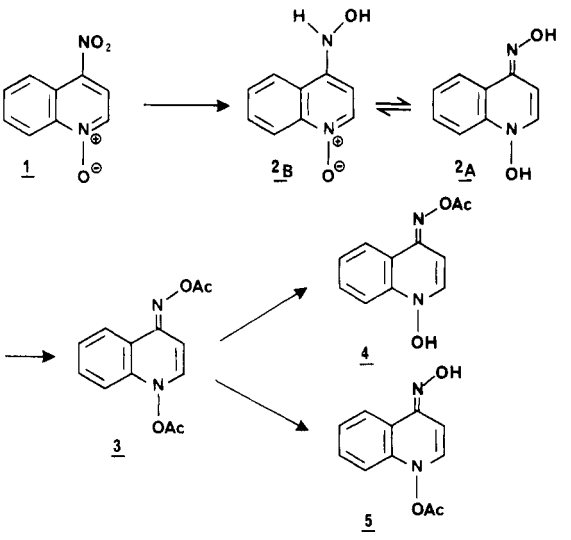
1-Hydroxy-4-(acetoxyimino)-1,4-dihydroquinoline is obtained quantitatively by reaction of 1-acetoxy-4-(acetoxyimino)-1,4-dihydroquinoline with piperidine in dimethyl sulfoxide. Spectroscopic results establish that this monoacetate exists preferentially as a hydroxylamine tautomer rather than as an *N*-oxide in the pH range 2–9, but below pH 2 protonation affords the N-protonated ester and above pH 9 an anion is formed. Hydrolysis below pH 2 gives clearly 4-(hydroxyamino)quinoline 1-oxide, which is also the major hydrolysis product at pH >9. In the intermediate zone pH 2–9 the neutral acetate affords a variety of products, including those of substitution at the 3-position, via the breaking of the N–O bond. By study of the rate of solvolysis of the neutral acetate in different solvents, applying the Grunwald Winstein relation, and by comparison with the solvolysis of the model compounds 4-(acetoxyamino)quinoline and [[[(*p*-nitrophenyl)sulfonyl]oxy]amino]quinoline, it is concluded that for the latter solvolysis proceeds via the intermediacy of nitrenium ions. Similarly solvolysis of 1-hydroxy-4-(acetoxyimino)-1,4-dihydroquinoline gives nitrenium ion intermediates with enhanced rates attributed to the accelerating influence of the *N*-oxide functionality.

A number of derivatives of aromatic amines are known to be powerful carcinogens. It is generally recognized that their mode of action involves the ultimate carcinogen reacting in a covalent manner with DNA.[1] The exact nature of the ultimate carcinogens derived from these derivatives of aromatic amines has been an area of extensive study. Thus in investigations of derivatives of 2-aminofluorene, 4-aminobiphenyl, and 2-aminonaphthalene it has been established that products of oxidation, hydroxylamine derivatives, such as the *N*-acetyl-*N*-acetoxyamines, react with DNA bases.[2] It has been proposed that similar hydroxylamine derivatives are the reactive metabolites of mutagenic aromatic nitro compounds.[3] In particular 4-nitroquinoline 1-oxide (**1**), a powerfully carcinogenic compound, and its metabolites have received sufficient attention to be the subject of a recent review.[4] It is well established that initial enzymatic reduction can lead to the hydroxylamine **2**,[5] which exists preferentially as the hydroxyimino tautomer[6] $\mathbf{2_B}$. It has been proposed that these tautomers are further metabolized to compounds able to bind to nucleic acid bases. In support of this hypothesis the diacetate **3** has been shown in in vitro experiments to react with DNA and with nucleosides[7] to give small amounts of products by covalent attachment to the bases. In particular a product with deoxyguanosine has been

Scheme I



[†] Université Joseph Fourier–Grenoble.
[‡] The University of Southampton.

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isolated and characterized. This product is also formed by reaction of the monoacetate **4** with the nucleoside and is formed as one of the many products from reaction with DNA in vivo.[8]

It is the objective of this and the following paper to study the formation of the two possible monoacetates **4** and **5** from the diacetate **3** in order to study their behavior with nucleophiles and hence to understand their possible reaction with nucleic acid bases. In this paper we report the study of the monoacetate **4** and relevant model compounds, which permits a better understanding of the key reaction intermediates, nitrenium ions. In the following paper[9] we describe the chemistry of the second monoacetate **5** and summarize the significance of the mechanistic conclusions, derived from the study of the esters **3–5**, with respect to the problem of carcinogenesis.

Earlier we have described the isolation of the monoacetate[10] **5** (as the crystalline hydrochloride) from the diacetate **3** and have described conditions that permit the quantitative conversion of the diacetate to the other monoacetate[11] **4**. These results, based on experiments showing the different behavior of the diacetate at various acidities (in 12 N hydrochloric acid the diacetate gives only the monoacetate **5**, which can be isolated in high yield; in 1 N hydrochloric acid the monoacetate **4** is formed as the only product; and in the range 9–3 N hydrochloric acid both monoacetates are formed), provide the foundation for the study of the chemistry of the two monoacetates. At that time we noted the hydrolysis of the two monoacetates to give inter alia the dihydroxy derivative **2**. Later our detailed study of the behavior of the monoacetate **4** has been published in preliminary form.[12] In this letter we were able to establish the intermediacy of nitrenium ions in the decomposition of this monoacetate, a conclusion of particular interest in view of the postulated intermediacy of nitrenium ions in the induction of cancer. In order to substantiate this conclusion we were led to compare the solvolytic behavior of the acetate **6** with that of the monoacetate **4**. In particular we chose to make a kinetic study based on a Grunwald Winstein analysis.[13] Although many such studies have been made for reactions proceeding via carbenium ion intermediates, our present study is the first application of the Grunwald Winstein relation to reactions proceeding via nitrenium ion intermediates. It was therefore of some interest to directly compare the ester **4** with the ester **6**. A further advantage of this comparison might have been a clarification of the role of the *N*-oxide function in the solvolytic behavior of the monoacetate. However, the model compound **6** proved to be too unreactive to permit useful solvolytic studies. Instead we describe in this paper the behavior of the more reactive ester **7**. The comparisons described below permit the conclusion that the *N*-oxide function has a powerful role in enabling the monoester **4** to react via a nitrenium ion intermediate.

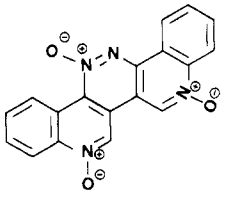
Results

Starting Materials. Three esters were required as reactants for the subsequent study. The monoester **4** is readily available from the diacetate **3**, which has been described previously.[11,14] By reaction of the diacetate dissolved in dimethyl sulfoxide with the stoichiometric quantity of piperidine, the monoacetate **4** is formed quantitatively (^{1}H NMR). Dilution of this solution with the appropriate solvent gave solutions of the monoacetate **4**, which could be used in kinetic experiments.

The acetate **6** was prepared in an unexceptional manner via the literature procedure of Hamana.[15-16]

The sulfonate ester **7** was prepared from the hydroxylamine **8** by a routine sulfonylation.

Product Studies. Under different hydrolytic conditions the monoacetate **4** gives a number of products. Thus in strongly acidic conditions, as reported elsewhere,[11] the dihydroxy derivative **2** is formed. This product is unstable in these conditions and decomposes partially during isolation and purification, but the proof of structure is based on the spectroscopic (^{1}H NMR and UV) characterization and chromatographic behavior by comparison with an authentic sample.[6] In weaker acidic conditions (0.1 N hydrochloric acid) the *N*-oxide **9** is obtained in high yield. This compound could be isolated by chromatography and characterized spectroscopically (MS, ^{1}H NMR, IR, and UV). It has previously been described by Sawanishi et al.[17] who, however, give little spectral data. In yet more dilute acidic conditions (0.01 N hydrochloric acid) other minor products are formed. One of these, the aminoquinoline *N*-oxide **10**, could be isolated and was characterized (MS, HPLC, and TLC) by comparison with an authentic sample.[17] In alkaline and at a neutral pH some other products are formed as noted elsewhere.[11] Such products (**16** and **17**) have also been obtained by other authors in studies of the dihydroxy derivative **2**.[18] These products have proved difficult to characterize and are the subject of further comment in the following paper.[9]



17

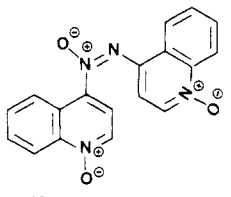


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Table I

Characteristics of the Hydrolysis of the Monoacetate 4						
	conditions of hydrolysis $[H^+]^a$					
	6 N	3 N	2 N	N	0.1 N	10^{-2} N
2, %	100	84	77	65	5	0
9, %	0	5	15	31	100	41
$k_{25°C}$ (s^{-1}) × 10^4	5.71 ± 0.25	2.15 ± 0.05	1.62 ± 0.03	1.01 ± 0.02	2.97 ± 0.08	18.00 ± 5.00
r^c	0.996	0.998	0.998	0.998	0.998	*d*

Characteristics of the Hydrolysis of the Acetate 6[b]			
	conditions of hydrolysis $[H^+]^a$		
	6 N	3 N	1 N
$k_{25°C}$ (s^{-1}) × 10^4	4.95 ± 0.10	1.83 ± 0.05	0.68 ± 0.01
r^c	0.999	0.998	0.998

[a] Measurements were made on solutions (4×10^{-3} M) at 25 °C. [b] The (hydroxylamino)quinoline **8** is the only product formed in acidic conditions. [c] "*r*" correlation coefficients for a linear treatment of concentration versus time data. [d] Rate extrapolated from only three points.

On hydrolysis in dilute hydrochloric acid the acetate **6** quantitatively gives the (hydroxyamino)quinoline **8**, which was characterized (^{1}H NMR, HPLC, and TLC) by comparison with an authentic sample.[15]

Under other solvolytic conditions a number of further products were formed and characterized. Thus in methanol the monoacetate **4** gave the two new compounds: the ether **11** and the acetate **12**. The former is sufficiently stable that it was isolated and characterized spectroscopically (MS, ^{1}H NMR, and UV). The latter, however, was much less stable and could not be fully characterized. However, it was found that this acetate **12** was also formed in *tert*-butyl alcohol, but on further reaction in this solvent afforded the amide **13**. This amide **13** was characterized (MS and ^{1}H NMR), and further analysis (HPLC) firmly established the formation of **12** from the acetate **4**. It is interesting to note from HPLC analysis that the acetate **12** is the major product in nonpolar solvents (e.g. *tert*-butyl alcohol or acetone–water (9:1)), but in more polar solvents much less of this product is observed.

The acetate **6** is stable in methanol but in trifluoroethanol–water (97:3) gives quantitatively the expected (hydroxyamino)quinoline **8** described above.

The sulfonate ester in methanol gives two new products: the ether **14** and the ester **15**. Both were isolated and fully characterized (MS, ^{1}H NMR, and UV). In trifluoroethanol–water (97:3) the ester **15** and the hydroxy derivative **18** are obtained.

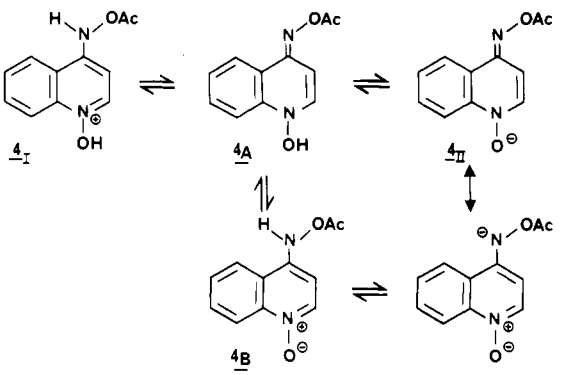
Kinetic Studies. Reactions in aqueous solution leading in the case of the monoacetate **4** to mainly the hydrolysis product **2** and the *N*-oxide **9**, and in the case of the acetate **6** to the hydroxylamine **8**, were followed by observation (HPLC) of the loss of the starting compounds and the formation of the products. First-order kinetics was observed for the loss of both **4** and **6** leading to the first-order rate constants shown in Table I. At pH 2 the product balance for the monoacetate **4** is poor due to the intervention of other reactions (see Discussion), but in more acidic conditions the product balance for the monoacetate **4** is good; similarly, formation of the hydroxylamine **8** fully accounts for the loss of the acetate **6**.

The acetate **6** was too unreactive to permit solvolyses to be studied either in alcoholic solvents or in mixtures of acetone–water. However rates were measured for the loss of the monoacetate **4** and the sulfonate ester **7** in various solvents.

Discussion

Although the behavior of the ester **4** has been studied through a large acidity range, probably the most significant region from a biological viewpoint is the region that is nearly neutral. However, in order to fully understand the solvolytic behavior of the ester **4** in this region, we first discuss our results in more extreme regions of acidity and basicity.

The reactivity of the monoacetate **4**, prepared from the diacetate **3** by use of a thiol, or piperidine, is complicated by the tautomeric equilibrium involving the tautomers 4_A and 4_B. Our results indicate that tautomer 4_A is the more



stable in dimethyl sulfoxide. Distinction between the two possible tautomers can be made by observation of $J_{2,3}$, and further support comes from other ^{1}H NMR data. In an *N*-oxide such as 4_B, the expected $J_{2,3}$ is 6–7 Hz. In the tautomeric form 4_A, literature data[19] indicate that $J_{2,3}$ should be larger ($J > 8$ Hz). Our observation that $J_{2,3}$ = 8 Hz hence suggests the presence of the tautomer 4_A. The observation of H-8 at 7.34 ppm in the monoacetate **4** is in good agreement with this assignment. In quinoline *N*-oxides the deshielding effect of the *N*-oxide group[6] leads to observation of H-8 at about δ = 8.45 ppm. In contrast H-8 is expected from literature precedent to be less deshielded in the tautomer 4_A (typical range 7–7.6 ppm).[6] As discussed more fully later it is considered that the various solvolytic products observed from the monoacetate **4** originate from reaction of the minor tautomer 4_B present in equilibrium with the dominant tautomer 4_A. Similarly 4-(acetoxyamino)quinoline **6** and the sulfonate ester **7** are characterized by possible tautomeric equilibria relating the species 6_A and 6_B, and 7_A and 7_B, respectively. Observation of $J_{2,3}$ = 7.5 Hz in the ester **6** again suggests the preference for the tautomer 6_A.

A second complication in the study of the monoacetate **4** concerns the possible behavior as a base and as an acid.

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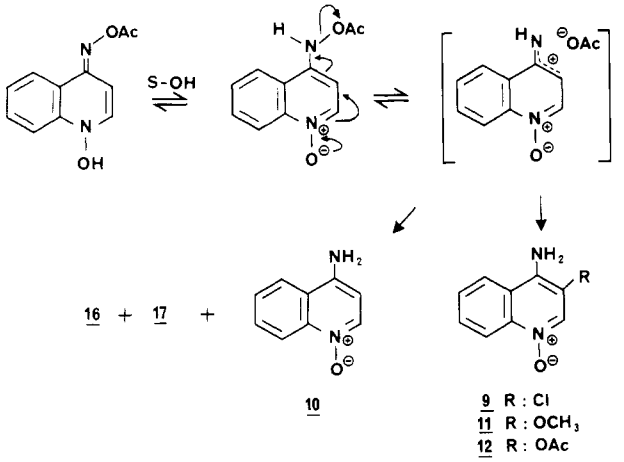
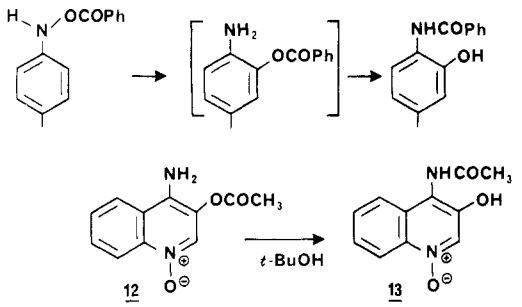
Scheme II



Scheme III



However, analysis of the UV spectra of the monoacetate **4** as a function of acidity leads to the observation of three types of spectrum. At low pH (pH <1) two maxima are observed at 232 and 332 nm, in an intermediate pH range maxima are observed at 260 and 365 nm, and at high pH (pH >10) the maxima are observed at 262 and 400 nm. Hence it is concluded that below pH 2 the protonated ester 4_I is the major species in solution, and above pH 9 the anion 4_{II} is the major species in solution. Only between pH 2 and pH 9 does the tautomeric equilibrium complicate the solvolytic behavior of the ester **4**.

Below pH 2 the major reaction of the ester 4_I is hydrolysis to give the dihydroxy derivative **2**. This is a clean reaction, which occurs to the exclusion of other processes observed at a higher pH. It is concluded that this hydrolysis involves an unexceptional acid-catalyzed attack on the ester function. In this pH range the ester **6** similarly undergoes hydrolysis to give the hydroxylamine **8**.

Above pH 10 the hydrolysis of the ester 4_{II} to give the same dihydroxy derivative **2** is probably the dominant process. However the analysis of this reaction is complicated by the instability of the product under these reaction conditions. The dihydroxy derivative **2** in basic media, as described elsewhere,[11] gives a complex mixture of products.[18]

In the intermediate pH range (pH 2–9), apart from formation of the dihydroxy derivative **2**, other products are formed.

In aqueous hydrochloric acid the *N*-oxide **9** is observed. Similarly solvolysis in other solvents leads to products by substitution at the 3-position. Other products such as the amine **10** are also formed in water. It is clear (see Table I) that in this intermediate pH range the importance of the hydrolytic processes, characteristic of the extreme pH ranges and described above, diminish, and a new series of reactions become dominant. These reactions of the neutral monoacetate **4** involve the breaking of the N–O bond and

Table II

Pseudo-First-Order Rate Constants for Solvolysis of Ester 4

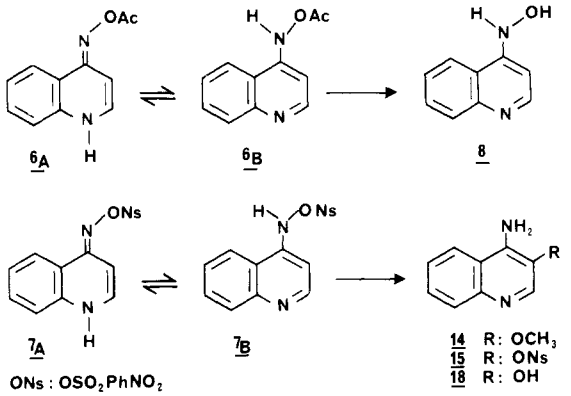
solvent	Y_{OTs}[a]	Y_{Cl}[b]	$k_{25°C}$ (s^{-1}) × 10^4	r[c]
EtOH	−1.75	−2.50	2.33 ± 0.08	0.994
MeOH	−0.92	−1.20	3.50 ± 0.25	0.996
EtOH–20% H_2O	0	0	7.22 ± 0.16	0.998
TFE–3% H_2O	+1.83	+2.83	47.31 ± 3.50	*d*
Me_2CO–H_2O				
90–10			2.69 ± 0.04	0.999
80–20		−0.80	5.58 ± 0.05	0.999
70–30		+0.17	8.50 ± 0.15	0.998
60–40	+0.66	+1.00	1.22 ± 0.42	0.999

Pseudo-First-Order Rate Constants for Solvolysis of Ester 7

solvent	Y_{OTs}[a]	N_{OTs}[a]	$k_{25°C}$ (s^{-1}) × 10^4	r[c]
MeOH	−0.92	−0.04	0.06 ± 0.001	0.997
EtOH–20% H_2O	0	0	0.11 ± 0.005	0.992
TFE–3% H_2O	1.83	−3	1.87 ± 0.02	0.999
TFE–50% H_2O	2.14	−0.93	2.68 ± 0.06	0.998
HFIP	3.79	−4.27	26.57 ± 0.31	0.999

[a] Reference 28. [b] Reference 29. [c] "*r*" correlation coefficients for a linear treatment of concentration versus time data. [d] Rate constant extrapolated from only three points.

Scheme IV



lead to the products **10**, **16**, **17** in Scheme II. In order to better understand the mechanism of such a bond breaking, the solvolysis of the monoacetate **4** was studied in other solvents.

From the results in Table II it can be seen that the monoacetate **4**, by reactions following pseudo-first-order kinetics, gave products at a rate determined by the ionizing power of the solvent. Application of the Grunwald Winstein relation[13] led to an excellent correlation (r = 0.996) with an m value (log $k/k_0 = mY$) of 0.36. As to our knowledge there are no related values in the literature; we would have liked to find the m value for a model system such as the solvolysis of the acetate **6**. However, as shown in Table II, this acetate is so unreactive even in trifluoroethanol that this is not possible, and a product study showed that the acetate **6** only gave the hydroxylamine **8** by attack at the ester group unlike the monoacetate **4**. Hence we turned to the sulfonate ester **7**, which although limited as a model by consequence of the change in leaving group, nevertheless could be used as an interesting model compound. In Table II results show that again by pseudo-first-order reaction this ester **7** reacts at a rate determined by the ionizing power of the solvent. A satisfactory Grunwald Winstein correlation leads to a somewhat higher m value (0.57). The products from the ester **7** (see Scheme IV) include substitution products at the 3-position.

The above observations indicate that in both the monoacetate **4** and the model sulfonate ester **7** reaction in the different solvents is via formation of a nitrenium ion intermediate. In particular the kinetic data point to charge

Table III. Compared Rates of Solvolysis of Esters 4, 6, and 7 in Trifluoroethanol–Water, 97:3

	$k_{25°C}$ (s^{-1})	k_{rel}
acetate 4	$(4.73 \pm 0.35) \times 10^{-3}$	462[a]
acetate 6	$(9.38 \pm 0.13) \times 10^{-6}$	1[b]
nosylate 7	$(1.87 \pm 0.02) \times 10^{-4}$	19[a]

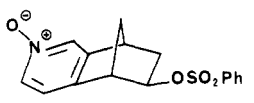
[a] Products resulting exclusively from N–O cleavage. [b] Solvolysis yields exclusively the (hydroxylamino)quinoline. No product resulting from N–O cleavage is formed.

separation in a transition state, and the identification of 3-substituted products, notably the ester **12** and **15** corresponding to ion pair return, indicate the intermediacy of nitrenium ions. Earlier studies with simpler systems give similar products, and are recognized to proceed via nitrenium ion intermediates.[20]

In the more complex case of the monoacetate **4** we consider that initial tautomerization of 4_A gives 4_B, which is a reactive intermediate affording the nitrenium ion intermediate and hence the products. It is most unlikely that tautomer 4_A would ionize to give an iminium cation. The requirement of tautomerization prior to ionization explains the behavior of the monoacetate **4** in different solvents. In aprotic solvents such as dimethyl formamide or dimethyl sulfoxide tautomerization is very slow and hence tautomer 4_A is stable. In protic solvents the tautomer 4_B is formed, and the rate of decomposition of the monoacetate is determined by the ionizing power of the solvent facilitating formation of the nitrenium ion. Similar considerations suggest that the sulfonate ester **7** also reacts via the tautomer 7_B to give a nitrenium ion. The obtention of substitution products, e.g. **12**, and of reduction, e.g. **10**, is characteristic of the behavior of nitrenium ions.[21]

The comparison of rate data (see Table III) for the three esters **4**, **6**, and **7** indicates a considerable enhancement in the reactivity of the monoacetate **4** relative to the acetate **6**. The latter does not give any products suggesting reaction via a nitrenium ion intermediate. Only the more reactive sulfonate ester **7** gives such products. From the monoacetate **4** and the sulfonate **7**, products are obtained indicative of a competition between ion pair return and participation of an external nucleophile (e.g. chloride in the case of **9**). The great reactivity of the monoacetate **4** can be attributed to the direct conjugative interaction of the *N*-oxide function with the nitrenium ion leading to substantial rate acceleration in the ester **4**. Indeed this observation may have a wider significance. The *N*-oxide function is a prerequisite for observed biological activity in the compounds of the aminoquinoline series. Only those compounds having an *N*-oxide function show carcinogenic activity.[4]

The rate acceleration that we attribute to the *N*-oxide function has recent literature precedent. Tanida et al.[22] have shown in the ester **19** and related compounds that the *N*-oxide function can accelerate solvolysis proceeding via carbocation intermediates. However their observed



19

modest acceleration is much less than that observed in our case. It is also well known that the *N*-oxide function facilitates electrophilic substitution in heterocyclic system.[23] Hence it is not surprising that the monoacetate **4** by activation by the *N*-oxide function has a comparable reactivity to the sulfonate ester **7** having the better leaving group.

Experimental Section

General Procedures. ^1H NMR spectra were recorded on a Bruker WP 60 (60 MHz). Chemical shifts are reported in ppm (δ) relative to hexamethyldisiloxane as internal standard. Mass spectra were recorded on a Riber-Mag 10-10 and a Varian MAT 311. UV spectra were recorded on a Beckman DB-GT and a Perkin Lambda 15. IR spectra were recorded on a Perkin-Elmer 237. Melting points are uncorrected. Reversed-phase HPLC was performed with a μ-Bondapak C18 analytical column (Waters Associates) equipped with a Model 660 solvent programmer and two M-6000 pumps (Waters Associates). The effluent was analyzed by a dual wavelength detector (254, 365 nm). A linear gradient of solvents was used from 10 to 100% methanol in water, pH 2.5 (phosphoric acid), during 10 min with a 2 mL/min flow rate.

Preparation of Starting Materials and Reference Compounds. 1-Hydroxy-4-(hydroxyimino)-1,4-dihydroquinoline (2) was prepared in 86% yield by reduction of the 4-nitroquinoline 1-oxide with ascorbic acid as described by Enomoto et al.:[24] mp 202 °C (lit.[24] mp 212 °C); UV max λ nm (1 N HCl) 340 (ϵ = 17 000), 232 (ϵ = 18 000); ^1H NMR (DMSO-d_6, DCl) δ 8.60 (d, 1 H, J = 8 Hz, H-2), 8.40 (m, 1 H, H-5), 7.50–8.05 (m, 3 H), 6.80 (d, 1 H, J = 8 Hz, H-3).

1-Acetoxy-4-(acetoxyimino)-1,4-dihydroquinoline (3) was prepared by acetylation of **2**[14] in 70% yield: mp 110–111 °C (lit.[14] mp 110 °C); ^1H NMR (DMSO-d_6) δ 8.10 (m, 1 H), 7.65 (d, 1 H, J = 8.5 Hz, H-2), 7.10–7.50 (m, 3 H), 6.15 (d, 1 H, J = 8.5 Hz, H-3), 2.40 (s, 3 H, $COCH_3$), 2.15 (s, 3 H, $COCH_3$).

1-Hydroxy-4-(acetoxyimino)-1,4-dihydroquinoline (4) was prepared as previously described[12] by acetyl transfer from **3** to piperidine or thiophenol: UV max λ nm (H_2O, NaOH, pH 10) 400 (ϵ = 16 000), 262 (ϵ = 14 000), λ nm (HCl pH 0.1), 332 (ϵ = 16 000), 232 (ϵ = 24 000), λ nm (EtOH) 365 (ϵ = 16 000), 260 (ϵ = 14 000); ^1H NMR (DMSO-d_6) δ 8.05 (m, 1 H), 7.10–7.70 (m, 4 H, Ar H and H-2), 6.05 (d, 1 H, J = 8 Hz, H-3), 2.10 (s, 3 H, $COCH_3$); chromatography (HPLC) of the monoacetyl derivative **4** showed two major peaks, which correspond to decomposition products formed on the column. Control experiments establish that those two unknown products are formed nearly quantitatively.

4-(Hydroxyamino)quinoline (8) was synthesized in a quantitative yield as described by Hamana:[15] mp 100–101 °C; UV max λ nm (EtOH) 342 (ϵ = 28 000), 332 (ϵ = 27 500), 230 (ϵ = 24 500); ^1H NMR (DMSO-d_6) δ 7.90 (m, 1 H), 7.00–7.30 (m, 4 H, Ar H and H-2), 6.15 (d, 1 H, J = 7.5 Hz, H-3); characterized as the hydrochloride, mp 260–262 °C (lit.[15] mp 262–263 °C).

4-(Acetoxyamino)quinoline (6) was synthesized by acetylation of **8** with acetic anhydride and imidazole in dimethylformamide[16] in 60% yield: mp 176–177 °C (lit.[25] mp 175–178 °C); ^1H NMR (DMSO-d_6) δ 10.90 (s, 1 H, N-H), 8.05 (m, 1 H), 7.10–7.60 (m, 4 H), 6.10 (d, 1 H, J = 7.5 Hz, H-3), 2.15 (s, 3 H, $COCH_3$).

4-[[[(*p*-Nitrophenyl)sulfonyl]oxy]amino]quinoline (7). To a stirred solution of 4-(hydroxyamino)quinoline (**8**) (0.5 g, 3.12 mmol) in pyridine (10 mL), which was cooled to near 0 °C (*p*-nitrophenyl)sulfonyl chloride (0.7 g, 3.15 mmol) was added. The solution was kept overnight at −20 °C, poured into water, and stirred in an ice bath. The yellow precipitate was filtered, washed twice with water and twice with ether, and then dissolved in ethyl acetate (100 mL). The resulting solution was dried over mag-

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nesium sulfate and filtered. Compound **7** was crystallized by addition of hexane to the ethyl acetate solution in 70% yield: mp 110–112 °C dec; UV max λ nm (EtOH) 348 (ε = 12 000), 262 (ε = 17 100), 246 (ε = 19 600), 214 (ε = 38 600); IR (KBr) 3480, 1635, 1530, 1500, 1455, 1365, 1350, 1315, 1190, 1090, 795, 765, 745, and 685 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.45 (s, 1 H, N-H), 8.10–8.50 (m, 4 H, SO_2PhNO_2), 7.00–7.85 (m, 5 H), 6.10 (d, 1 H, J = 7.5 Hz, H-3); HRMS calcd 345.0419, found 345.0422. Anal. Calcd for $C_{15}H_{11}N_3O_5S$: C, 52.17; H, 3.21; N, 12.17; O, 23.16. Found: C, 52.11; H, 3.07; N, 12.17; O, 23.72.

4-Aminoquinoline 1-Oxide (10). The 4-chloroquinoline 1-oxide (0.5 g, 3.1 mmol) was dissolved in methanol (15 mL) saturated with ammonia and was heated at 125 °C in a sealed tube for 7 h. The solvent was then evaporated, and the aminoquinoline 1-oxide **10** was separated by column chromatography on alumina (eluant: chloroform–ethanol, 95:5): mp 272–273 °C dec (lit.[17] mp 274 °C); ^1H NMR (DMSO-d_6) δ 8.45 (m, 1 H), 8.05–8.30 (m, 2 H), 7.45–7.75 (m, 2 H), 6.80 (s, 2 H, NH_2), 6.45 (d, 1 H, J = 7.2 Hz, H-3); MS, m/e (relative intensity) 160 (M^+, 100), 144 (M^+ – 16, 49), 131 (45), 129 (7), 117 (41), 116 (43).

3-Chloro-4-aminoquinoline 1-Oxide (9). The diester **3** (0.05 g, 0.19 mmol) was suspended in 10^{-2} N aqueous hydrochloric acid. The solution was stirred at room temperature until all the starting material had dissolved. The solvent was then evaporated to dryness, and the residue was chromatographed (PTLC) to give the rather unstable 3-chloro-4-aminoquinoline 1-oxide **9**: UV max λ nm (MeOH) 370 (ε = 10 800), 260 (ε = 16 500), 224 (ε = 30 500) (lit.[17] UV max λ nm (MeOH) 372 (ε = 8750), 260 (ε = 12 300), 223 (ε = 27 600)); ^1H NMR (DMSO-d_6) δ 8.10–8.20 (m, 2 H), 8.40 (s, 1 H, H-2), 7.50–7.80 (m, 2 H), 7.00 (s, 2 H, NH_2).

3-Hydroxy-4-(acetylamino)quinoline 1-Oxide (13). To the diester **3** (0.126 g, 0.48 mmol) dissolved in dimethyl sulfoxide (1 mL) was added piperidine (0.05 mL, 0.5 mmol). The mixture was diluted with *tert*-butyl alcohol (250 mL) and left for 20 h at room temperature in the dark. After concentration of the solvent to 30 mL, the 3-hydroxy-4-(acetylamino)quinoline 1-oxide **13** was precipitated by adding a large volume of ether in 48% yield: mp 232–233 °C dec; UV max λ nm (H_2O, pH 7) 360, 240, λ nm (1 N HCl) 350, 240, λ nm (1 N NaOH) 395, 251; IR (KBr) 3250, 3000, 1655, 1490, 1365, 1270, 1210, 1170, and 1125 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.70 (broad s), 8.30–8.40 (m, 2 H), 7.50–7.70 (m, 3 H), 2.10 (s, 3 H, $COCH_3$); HRMS calcd for $C_{11}H_{10}N_2O_3$ 218.0691, found 218.0697.

3-Methoxy-4-aminoquinoline 1-Oxide (11). The diester **3** (100 mg, 0.38 mmol) dissolved in methanol (200 mL) was kept for 3 days at room temperature in the dark. The solution was then evaporated to dryness, and the residue was purified by chromatography (eluant: ethylacetate–ethanol, 4:3) to give as the main product 3-methoxy-4-aminoquinoline 1-oxide (**11**), isolated in 40% yield: mp 205 °C (lit.[26] mp 226–228 °C); UV max λ nm (H_2O, pH 5.5) 375, 264, λ nm (NaOH, pH 12) 375, 260, λ nm (HCl, pH 1) 355, 252; IR ($CHCl_3$) 3410, 2830, 1625, 1590, and 1340 cm^{-1}; ^1H NMR (DMSO-d_6, 270 MHz) δ 8.35 (s, 1 H, H-2), 8.30 (d, 1 H, J = 9 Hz, H-8), 8.15 (d, 1, H, J = 9 Hz, H-5), 7.20–7.55 (m, 2 H), 6.35 (s, 2 H, NH_2), 3.80 (s, 3 H, OCH_3); HRMS calcd for $C_{10}H_{10}N_2O_2$ 190.0742, found 190.0749.

3-(Nosyloxy)-4-aminoquinoline (15) and 3-Methoxy-4-aminoquinoline (14). The nosylate derivative **7** (0.33 g, 0.95 mmol) was dissolved in methanol (150 mL) and stirred at room temperature in the dark for a week. After evaporation of the solvent under reduced pressure, the residue was chromatographed to afford as the less polar fraction (eluant: ether) compound **15** in 30% yield [mp 226–227 °C; IR (KBr) 3480, 3440, 3360, 3220, 1660, 1635, 1590, 1530, 1445, 1405, 1380, 1350, 1315, 1290, 1200, 1180, 1140, 1090, 930, 875, 815, 765, and 750 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.00–8.50 (m, 6 H, SO_2PhNO_2, H-2 and H-5), 7.20–7.70 (m, 3 H), 6.80 (s, 2 H, NH_2); HRMS calcd for $C_{15}H_{11}N_3O_5S$ 345.0419, found 345.0422]; and as the more polar fraction (eluant: ethylacetate–ethanol–triethylamine, 90:10:1) 3-methoxy-4-aminoquinoline (**14**) in 30% yield: mp 152–153 °C (lit.[26] mp 155 °C); IR (Nujol) 3440, 3380, 3120, 1630, 1590, 1565, 1510, 1490, 1370, 1315, 1280, 1240, 1205, 1115, 1040, 905, and 760 cm^{-1}; ^1H NMR (CD_3OD) δ 8.30 (s, 1 H, H-2), 8.05 (m, 1 H, H-5), 7.30–7.80 (m, 3 H), 3.95 (s, 3 H, OCH_3); MS, m/e (relative intensity) 174 (M^+, 71), 159 (76), 144 (2), 131 (100), 116 (11). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.50; H, 5.84; N, 15.97.

3-Hydroxy-4-aminoquinoline (18). Product **7** (0.1 g, 0.29 mmol) was dissolved in trifluoroethanol (10 mL), and the solution was diluted with water (10 mL). The reaction mixture was stirred in the dark at room temperature for a week. The solvent was then evaporated to dryness under reduced pressure to afford a residue, which on chromatography gave as the less polar fraction (eluant: ether) compound **15** as previously described in 20% yield and as the more polar fraction (eluant:ethanol–triethylamine, 97:3) 3-hydroxy-4-aminoquinoline (**18**) in 28% yield: mp 160 °C dec (lit.[27] mp 119 °C); UV max λ nm 267 (ε = 13 100), 247 (ε = 16 500), 216 (ε = 14 100); IR (KBr) 3380, 3200, 1165, 1645, 1560, 1500, 1485, 1380, 1285, 1230, 1020, 760, and 655 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.25 (s, 1 H, H-2), 8.00–8.20 (m, 1 H, H-5), 7.20–7.70 (m, 3 H), 6.15 (s, 2 H, NH_2); HRMS calcd for $C_9H_8N_2O$ 160.0633, found 160.0637.

Methodology for Kinetic Experiments. Solvolyses were studied under a variety of conditions including studies in aqueous media and in organic solvents. For experiments in aqueous acid at or below pH 2, hydrochloric acid was used. Between pH 3 and 7, citrate phosphate or acetate buffers were used. At a higher pH dilute solutions of sodium hydroxide were used. The following organic solvents were used: mixtures of acetone–water (see Table II) and a variety of alcohols.

All kinetics were performed at 25 ± 0.5 °C in the dark and were monitored by HPLC. The concentrations of esters were 5.2 × 10^{-3} and 2.8 × 10^{-3} M, respectively, for the acetate **6** and nosylate **7** derivatives. They were obtained by dissolving the ester (10 mg) in the appropriate solvent (10 mL). Solutions of monoester **4** were obtained by dissolving the diester **3** (10 mg, 0.038 mmol) in dimethyl sulfoxide (0.2 mL). A stoichiometric amount of piperidine (4.5 × 10^{-3} mL, 0.04 mmol) was added to the solution, which turned bright yellow. After 3 min, the solution was diluted by the appropriate solvent (10 mL) to give a final concentration of 3.7 × 10^{-3} M in monoester **4**.

The disappearance of the starting material and the formation of reaction products were monitored as a function of time by removing aliquots (5 μL) and introducing them onto the HPLC column. Peak heights or peak areas (recorded on a Waters Associates Data Module) were used to determine pseudo-first-order rate constants. All solvolyses were followed up to 95% conversion, and duplicate experiments were always run. Average first-order-rate constants were reported with average deviation of ±5%. In all the experiments controls established that each of the products could be quantitatively analyzed in a satisfactory manner. This was achieved by independent synthesis of pure samples and calibration of HPLC experiments. Although these compounds could be isolated in a pure state, their instability prevented an accurate determination of yields by product isolation. Instead yields are based on the HPLC experiments and are established to be reliable based on the control experiments.

For certain of the less stable compounds extra checks were made to establish their formation. For example, 4-(hydroxyamino)-quinoline 1-oxide **2** (formed in 6 N hydrochloric acid) was shown to have the same UV spectrum λ max 232 (ε = 18 600) and 342 (ε = 17 000) nm as an authentic sample and to have identical chromatographic behavior (TLC and HPLC). Similarly 3-chloro-4-aminoquinoline 1-oxide **9** was obtained by reaction of the monoacetate **4** in hydrochloric acid (0.1 N) for 5 h. Subsequent neutralization (0.1 N sodium hydroxide) and dilution with methanol afforded a solution having essentially the same UV spectrum (λ max 224 (ε = 30 500), 260 (ε = 16 500), and 370 (ε = 10 800) nm) as an authentic sample. 4-(Hydroxyamino)quinoline (**8**) formed from 4-(acetoxyamino)quinoline (**6**) could not be isolated in a pure state from this reaction. The authenticity of the product was established by chromatographic comparison (HPLC, TLC) with an authentic sample. Further proof was

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obtained by acetylation of the reaction product to give 4-(acetoxyamino)quinoline (**6**), shown to be identical (HPLC, TLC) with an authentic sample.

Reaction in neutral or basic conditions. pH 7: the monoester solution was diluted with 10 mL of 1 N acetate buffer solution. A precipitate was immediately formed; it was filtered and analyzed by mass spectrometry: MS, *m/e* (relative intensity) 314 (7), 298 (10), 284 (15), 282 (100), 270 (11), 254 (7), 141 (11), 127 (16). pH 10: the precipitate formed was analyzed by mass spectrometry: MS, *m/e* (relative intensity) 332 (4), 316 (6), 314 (2), 300 (8), 298 (4), 284 (20), 282 (12), 271 (5), 255 (5), 160 (14), 158 (14), 149 (27), 145 (58), 144 (26). pH 13: the 4-(hydroxyamino)quinoline 1-oxide **2** intermediately formed was analyzed by HPLC; it decomposed in the reaction conditions to give a red solid, analyzed by mass spectrometry: MS, *m/e* (relative intensity) 330 (1), 316 (4), 316 (1), 300 (17), 298 (4), 284 (85), 282 (26), 255 (23), 144 (17), 129 (80). The mass spectrum was identical with the one obtained by dissolving synthetic 4-(hydroxyamino)quinoline 1-oxide (**2**) in the same solvent.

Registry No. **1**, 56-57-5; **3**, 18061-48-8; **4**, 84752-93-2; **6**, 32654-59-4; **7**, 117940-74-6; **8**, 13442-05-2; **9**, 58550-85-9; **10**, 2508-86-3; **11**, 19701-39-4; **13**, 117940-75-7; **14**, 19701-38-3; **15**, 117940-76-8; **18**, 53972-05-7.

Concerning Model Metabolites of the Carcinogen 4-Nitroquinoline 1-Oxide. Reactivity of 1-Acetoxy-4-(hydroxyimino)-1,4-dihydroquinoline

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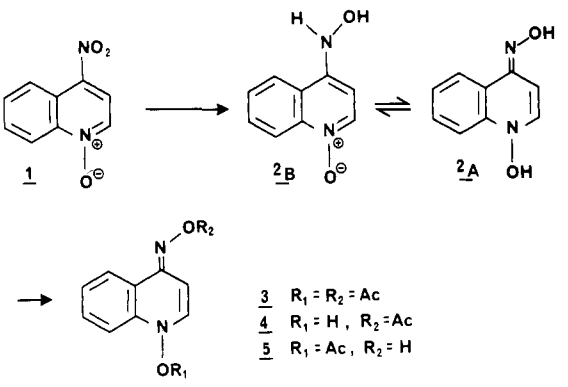
1-Acetoxy-4-(hydroxyimino)-1,4-dihydroquinoline is obtained quantitatively by hydrolysis of 1-acetoxy-4-(acetoxyimino)-1,4-dihydroquinoline under strongly acidic conditions. At pH <1 the monoacetate is protonated and on hydrolysis affords only 1-hydroxy-4-(hydroxyimino)-1,4-dihydroquinoline. Above pH 1 on hydrolysis the monoacetate affords a complex product mixture including 4-(hydroxyamino)quinoline and 4-nitrosoquinoline. Comparison of the above behavior of 1-acetoxy-4-(hydroxyamino)-1,4-dihydroquinoline with that of 1-hydroxy-4-(acetoxyimino)-1,4-dihydroquinoline at a neutral pH suggests that the former type of ester is less likely to be important in those steps initiating oncogenesis. In contrast the latter type of monoester or diesters corresponding to 1-acetoxy-4-(acetoxyimino)-1,4-dihydroquinoline by their ability to generate nitrenium ion intermediates and undergo attack by nucleophiles at the 3-position are likely intermediates in the process of oncogenesis. Further aspects of their likely biological role are discussed.

There has been great interest in the biology and the chemistry of 4-nitroquinoline *N*-oxide (**1**), which is one of the most potent and most studied of synthetic chemical carcinogens.[1] Reduction of the nitro group is a prerequisite for the initiation of oncogenesis by this compound.[2] Such a reduction may lead to the hydroxylamine **2**, capable of existing in the tautomeric forms $\mathbf{2}_A$ and $\mathbf{2}_B$.[3] It has been suggested that esters of the hydroxylamine **2** may be involved in the metabolic process leading to the observed oncogenesis.[4] As discussed in the accompanying paper,[5] these suggestions have stimulated our present work to understand the likely pathways open to diesters of the hydroxylamine **2**, such as the diacetate **3**, and to monoesters **4** and **5** (Scheme I). In the early part of our work,[6] we reported the behavior of the diacetate **3** and established that in different pH ranges the two monoacetates **4** and **5** were obtained as products. In the preceding paper[5] we report the hydrolysis of the monoester **4** and establish that under certain conditions solvolysis involves nitrenium ion intermediates. In this paper we now describe the quite different chemistry of the second monoacetate **5**. The reactivity of the monoester **4** is dominated by the activating effect of the *N*-oxide function. The absence of this effect in the monoester **5** leads to a contrast in the chemistry of the two series of monoesters. In the light of those results reported earlier[5,6] and in this paper, we are now able to comment further on the relationship between the chemistry of those derivatives of 4-nitroquinoline *N*-oxide, which have been postulated as metabolites, possibly involved in the initiation of oncogenesis, and the formation

Scheme I



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